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Biocontrol Strategy of Bacitracin Stabilization of the Fuel Ethanol Fermentation Process in Industries

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Abstract: Microbial contamination of industrial-scale bioprocesses, especially biofuel fermentations, has constantly posed serious threats to the production of bioproducts, causing losses in the economy, low production and instability in the process. Conventional control strategies such as antibiotics, chemical preservatives, and sterile filtration have weaknesses, i.e, cost, government regulations, customer opposition and emergence of resistant strains. Ribosomally synthesized antimicrobial peptides produced by bacteria (bacteriocins) have proven to be potential, sustainable and effective biocontrol agents. This is a summary of the recent articles in the field of application of bacteriocins to protect biofuel fermentations (primarily ethanol and butanol). We delve into their range of activity, their action against typical contaminants (lactic acid bacteria, wild yeasts, clostridia), their methods of use (in-situ synthesis by starter cultures, extrinsic addition, or transgenic producer strains), and their tolerance to process conditions. We weigh up the merits, such as target specificity, biodegradability and little effect on fermentation microbiota against the problems of production expenditure, stability in multifaceted fermentation broths and government acceptance. The incorporation and fusion of bacteriocins; in particular, using metabolic engineering and combinatorial synergies, is a change paradigm to more vigorous, efficient, and sustainable industrial biotechnology.

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1. Introduction

The Contamination Challenge in Industrial Bioprocesses (Expanded Academic Version).

The shift of the world to a circular bio economy has placed industrial biotechnology as the core foundation of the sustainable energy generation, whereby biofuel fermentations are the principal industrial application(1). The microbial biocatalysts, typically *Saccharomyces cerevisiae* in ethanol fermentations and *Clostridium acetobutylicum* or similar in acetone-butanol-ethanol (ABE) fermentations are essential to first generation bioethanol processes based on sugarcane and corn starch, second generation lignocellulosic bioethanol processes, and highly developed biofuels including biobutanol. In all of which a large scale of operation, nutrient-rich feeds, and continuous or discontinuous processing in non-sterile or semi-sterile conditions predetermines their predisposition to microbial contamination(2-4).

Economic limitations on the scale and industrial biofuel plants also have to work within a time constraint where high cell densities, turnaround times and reuse of process

streams dictate that microbes are exposed and that aseptic control is no longer feasible. There are various routes contaminating microorganisms with the main ones being raw feedstocks, recycled process water, poorly sanitized equipment, biofilms in pipelines and exposure of the material to air during the process of transfer. Contaminants introduced may easily develop because of good temperature, pH and nutrient factors, and may also have faster growth rates compared to the growth of the production microorganisms. This results in direct competition over fermentable sugars, essential nutrients, and growth factors and indirect competition by the buildup of inhibitory metabolites and quorum-sensing-mediated changes in the community(5).

On the level of the metabolic activity, poisoning microorganisms redirects the carbon flow off-pathway to the intended products and raises the cellular maintenance energy needs of the production strains(6). This leads to low biomass productivity, low fermentation kinetics, partial sugar utilization and accumulation of undesirable by-products. Moreover, the microbial interaction in mixed populations can increase adaptive stress responses, which further increases contaminant persistence, making it difficult to get rid of once contamination occurs(7).

The economically most important pollutants are:

Lactic Acid Bacteria (LAB):

The dominant contaminant bacteria in ethanol fermentations are genera *Lactobacillus*, *Pediococcus* and *Leuconostoc*. LAB convert glucose and other sugars to lactic and acetic acids, and this leads to the rapid fermentation broth acidification(8). This lowering of pH alters the metabolic activity of the yeast, distorts the integrity of the membrane, and redirects the flow of carbon towards other pathways instead of ethanol(9). Moreover, undissociated organic acids may also permeate the yeast cells and dissociate inside the cell, resulting in cytoplasmic acidification, oxidative stress and higher ATP using to extrude protons. LAB is also able to secrete bacteriocin-like inhibitory compounds and hydrogen peroxide which further inhibits yeast performance(10). Losses in the yield of ethanol have been reported between 1 and above 30 percent, prolonged fermentation, excessive formation of glycerol and repeated closure and re-initiation of the process because of LAB contamination(11).

Wild Yeasts: Non-Saccharomyces yeasts can withstand extreme industrial conditions and outcompete production strains in terms of carbon and nitrogen. Certain wild yeasts are more resistant to stressors that include low pH, high osmolarity, and high ethanol levels that enable them to survive during fermentation periods(12). They can also modify the flocculation behavior, enhance the formation of foams, and produce undesired metabolites including higher alcohols and organic acids which have adverse impacts on downstream operations and products(12, 13).

Acetic Acid Bacteria (AAB): *Acetobacter* and *Gluconobacter* are able to oxidize ethanol to acetic acid in the microaerophilic environment, which directly reduces the end ethanol, and which causes a greater amount of acid stress to fermentative organisms(14). They particularly cause a bad problem in fermentation systems allowing entry of oxygen into the fermentation during agitation or transfer operations(15).

Other Bacteria and Clostridial Contaminants: ABE fermentations may be contaminated with non solventogenic *Clostridium* or facultative anaerobes leading to the metabolic shift to acidogenesis rather than solventogenesis, reducing butanol productivity by many folds and placing the fermentation at risk of acid crash phenomena(16, 17). In addition, bacterial infection can be accompanied with bacteriophage infection, which can also destabilize solventogenic cultures(18, 19).

In addition to a decrease in yields, contamination has wider implications in operation such as higher viscosity of fermentation broths, a decrease in the effectiveness of mass transfer, foaming issues, plugging of heat exchangers, and higher energy consumption in the distillation process as a result of lower alcohol concentrations(20, 21). The effect of these problems is higher cost of operation, decreased throughput of the plant, and

reduction of equipment life. All these effects combined are translated to massive economic losses at industrial level and erode the sustainability of the biofuel production chains in totality.

Traditional contamination control measures have major weaknesses(22). Large fermentation volumes are very energy-consuming and not economically viable to heat sterilize. There has been extensive usage of antibiotics, like virginiamycin and penicillin(23), but there is a growing tendency to limit the use of these drugs because their application is also linked with the spread of antimicrobial resistance and increased regulatory constraints linked to animal feed by-products like distillers dried grains with solubles (DDGS) and the rising demand of the consumers to have antibiotic free bioprocesses. Furthermore, antibiotics can destabilize positive microbial communities and bias on the enduring contaminated resistant elements(24). Chemical biocides are efficient, although they are usually non-selective, may slow the production strain, and may present residual toxicity, equipment corrosion, and environmental hazards(25). The incidence and effect of microbial contaminants during fermentations of fuel ethanol have been examined in a few studies, as shown in Table 1.

Table 1. Central Research on Fuel Ethanol Production Microbial Contamination.

Study	Aim / Scope	Major Contaminants	Key Findings	Reference
Bacterial contaminants of fuel ethanol production	Commercial ethanol plant surveying to determine the prevalent bacterial contaminants.	<i>Lactobacillus</i> spp. (<i>L. fermentum</i> , <i>L. salivarius</i> , <i>L. casei</i>)	The predominant contaminants were lactic acid bacteria (LAB) which were linked with elevated organic acids and fermentation disruptions.	Bischoff et al., J. Ind. Microbiol. Biotechnol., 2004 (26)
Microbial contamination of fuel ethanol fermentations	Surveillance of the contamination sources and their effect on the yield of ethanol.	<i>Lactobacillus</i> spp., wild yeasts (<i>Dekkera bruxellensis</i>)	LAB and wild yeasts decrease the efficiency of fermentation, and they compete with <i>Saccharomyces cerevisiae</i> .	Applied Microbiology Reviews, 2011 (27)
Microbial contamination of commercial corn-based fuel ethanol fermentations	DNA-based analysis of microbial communities in industrial ethanol plants.	Mainly <i>Lactobacillus</i> spp., few fungal species	Contaminants persisted throughout processing stages, indicating limitations of sanitation procedures alone.	Rich et al., Bioresource Technology Reports, 2020 (28)
Biofilm formation and	Long-term monitoring of	<i>L. plantarum</i> , <i>L. casei</i> , <i>L.</i>	~92% of isolates were	Industrial Microbiology

Study	Aim / Scope	Major Contaminants	Key Findings	Reference
ethanol inhibition by bacterial contaminants	bacterial populations in an ethanol plant.	<i>mucosae</i> , <i>L. fermentum</i>	LAB; several strains formed biofilms and significantly inhibited ethanol production.	Study, 2015 (29)
Controlling bacterial contamination using lignin-derived bio-oils	Evaluation of antibiotic alternatives for controlling LAB contamination.	Antibiotic-resistant <i>Lactobacillus</i> spp.	Lignin bio-oils reduced LAB growth without affecting yeast and improved ethanol yield.	Kalinoski et al., Green Chemistry, 2021(30)
Selective suppression of bacterial contaminants by process conditions	Studied process conditions favoring yeast over bacteria in fermentation.	LAB and acetic acid bacteria	Adjusting NaCl and ethanol levels reduced bacterial counts while maintaining yeast performance.	Biotechnology for Biofuels, 2011(31)
Resolving bacterial contamination with beneficial bacteria	Use of beneficial LAB strains to suppress harmful contaminants.	Mixed LAB populations	Certain LAB strains restored fermentation efficiency, suggesting a probiotic-like control strategy.	Elsevier, 2017(32)
Effects of feedstock and co-culture of <i>L. fermentum</i> and wild yeast	Studied mixed contamination effects under different feedstocks.	<i>L. fermentum</i> and wild <i>S. cerevisiae</i>	Wild yeast had stronger negative effects than LAB in repeated-batch fermentations.	AMB Express, 2018(33)

Table 1 demonstrates that the lactic acid bacteria, especially *Lactobacillus* species, are always among the dominant populations of contaminants in ethanol plants and therefore there is an imminent need to have specific antimicrobial approaches that would be selective in that they would inhibit the lactic acid bacteria without negatively affecting the performance of the yeasts.

Here, bacteriocins come out as promising biocontrol agents. Bacteriocins are antimicrobial ribosomally transcribed peptides or proteins that are synthesized by bacteria, usually with an active effect against phylogenetically related bacteria(34). They are divided into Class I lantibiotics (e.g., nisin), Class II small heat-stable peptides (e.g.,

pediocin PA-1 and plantaricins), and Class III large heat-labile proteins(35). Their antimicrobial effect is mostly facilitated by formation or inhibition of cell wall biosynthesis or membrane pore formation which leads to quick cell death and less likelihood of development of resistance because of multi-target interaction(36). Notably, a great number of bacteriocins survive during acidic conditions, do not lose their activity at fermentation temperatures, and demonstrate low levels of toxicity to eukaryotic cells(37). Their narrow spectrum activity makes them selective to certain contaminants like LAB but non-selective to production organisms hence preserving fermentation performance and microbial balance(38). Besides, a number of bacteriocins have GRAS status, which eases the regulatory approval to use in industry(39). As such, bacteriocins are biologically compatible, environmentally friendly, and possibly cost-effective alternatives to traditional antimicrobial methods, and thus, they can be important elements of future contamination control systems in industrial biofuel fermentation, especially in combination with metabolic engineering and real-time process observation approaches(37).

2. Materials and Methods

Bacteriocins: Classification, Biosynthesis, and Mode of Action

Classification and Diversity

The most applicable bacteriocins to use in biofuels belong to the Class I and II. Nisin (Class I), the most studied and commercially available is produced by *Lactococcus lactis*. It has a wide spectrum of Gram-positive activity, such as LAB and clostridia. Other types of Class II bacteriocins such as pediocin PA-1 (*Pediococcus acidilactici*) and plantaricin (*Lactiplantibacillus plantarum*) can be more specific. Their strength is normally in single-digit nanomolar to micromolar(33).

Mechanisms of Antimicrobial Action

The major attack is on bacterial cytoplasmic membrane. The majority of the bacteriocins create pores, with the result of depolarization, collapse of the proton motive force, and efflux of essential cellular materials (cell death). Nisin is an example which attaches to Lipid II (a cell wall precursor) preventing cell wall synthesis and at the same time using it as a docking molecule of pore formation (33, 40). This interaction prevents the development of resistance(41). Their particularity is usually predetermined by the binding to a particular receptor on the target cell surface.

Application of Low-Molecular-Weight Bacteriocins in Fermentation Biocontrol in *Lactobacillus brevis*.

Various strains of *Lactobacillus brevis* have been identified to produce Class II bacteriocins of low molecular weight which are highly effective antimicrobials against closely related lactic acid bacterium and other Gram-positive contaminants regularly found in the industrial fermentations. These bacteriocins are heat-stable small peptides, typically between 3-6 kDa, and are active over a broad pH spectrum, and in high ethanol concentration, so they are especially likely to be useful in biofuel fermentation processes(42).

Mechanistically, *L. brevis* bacteriocins mostly cause their antimicrobial effect by forming a pore in the cytoplasmic membrane of target cells causing membrane depolarization, intracellular metabolite leakage, and cell death. Unlike general-purpose chemical antimicrobials, these peptides are selective in their inhibitory effect on other competing LAB species and have little or no effect on fermentative yeasts, including *Saccharomyces cerevisiae*(42). This is beneficial to selective pressure that ensures a high rate of ethanol productivity and inhibition of competing bacteria populations(42).

In practice terms, bacteriocins produced by *L. brevis* offer numerous possibilities of being incorporated in the process of industry. They can be used either as partially purified antimicrobial preparations or as part of fermentation systems by co-culture techniques with non-competitive producer strains or expressed in production microorganisms by

genetic engineering. Notably, various studies have shown that bacteriocins of *Lactobacillus* species have the capacity to withstand activity in complex fermentation broths and under the influence of organic acids and other inhibitory substances that are normally present in lignocellulosic hydrolysates(42, 43).

The low-molecular-weight bacteriocin isolation and characterization of *L. brevis* such as confirmation of their proteinaceous nature by sensitivity to proteolytic enzymes and molecular weight estimation offer the critical validation of their appropriateness as a biocontrol agent(44). Moreover, bioinformatic examination of bacteriocin gene clusters can facilitate the forecasting of peptide structure, immunity proteins, and transport systems in the name of sound plans of metabolic engineering and the best-induced expression in industrial host strains. All these findings indicate that using *L. brevis*-derived bacteriocins is valid as an antimicrobial product scaleable, stable and specific to preserve fermentation of industrial biofuels(45).

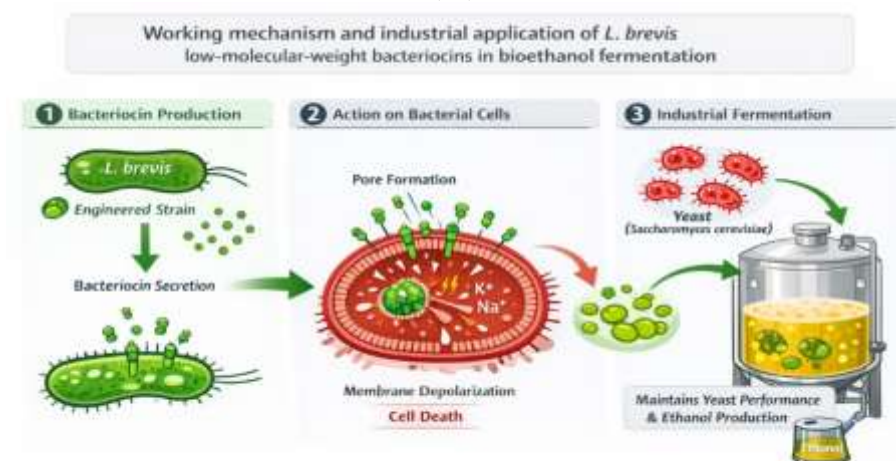


Figure 1. The mechanism of action and industrial use of low-molecular-weight bacteriocins produced by the bacteria, *Lactobacillus brevis*, during bioethanol fermentation.

The figure shows (1) the synthesis and release of bacteriocins by either natural or engineered producer strains, (2) the association of the bacteriocins with the cytoplasmic membrane of the contaminating lactic acid bacteria, subsequent pore formation, depolarization of the membrane, release of intracellular ions, and consequently cell death, and (3) the incorporation of bacteriocin-based biocontrol strategies into industrial fermenters to prevent bacterial contamination and maintain the activity and ethanol production of engineered producer strains.

Biofuel Fermentation Safeguarding Applications.

Control of Lactic Acid Bacteria in Ethanol Fermentations

Most of the applied research is aimed at inactivating LAB contamination in ethanol production using corn- or molasses-based fermentation processes, in which the competition of bacteria and organic acid buildup are the leading factors that lead to lower fermentation performance and product yield(46). LAB do not only drive fermentable sugars past ethanol production, but also produce metabolites that inhibit the production of ethanol and raise the maintenance energy demand of yeasts and lower ethanol tolerance(47).

Addition of Purified/Semi-purified Bacteriocins Exogenously: Ground-breaking experiments showed that the addition of nisin to fermentations in their pure state could prevent the growth of LABs. At low concentrations of 0.25 2.5 ppm (IU/mL), nisin was very effective in controlling the populations of *Lactobacillus* which resulted in increased ethanol production (45 percent) and less acid production(47, 48). Likewise, there was an

efficacy of pediocin PA-1 against certain spoilage LAB(49, 50). In addition to yield enhancement, bacteriocin supplementation has been demonstrated to stabilize the fermentation kinetics, shorten fermentation time, and stabilize fermentation variability between batches of production which is essential in continuous industrial process(51).

Besides this, bacteriocins can be used with standard process conditions like low pH and high ethanol content, and do not disrupt the metabolism of yeast or yielding distillation. Their compatibility enables them to be readily integrated in the existing industrial fermentation processes without undertaking any major process re-engineering(33).

In-Situ Production by Starter or Co-Culture Strains: The economic appeal is that, this method does not require expensive purification. One of the research thrusts has been to engineer the production yeast *S. cerevisiae* to express and secrete bacteria, bacteriocins. Nisin, pediocin PA-1 and other bacteriocins have been expressed successfully in yeast(52). Bacteriocin generation during fermentation using these engineered strains is constitutive and it forms a protective microenvironment around cells of yeast that inhibits the colonization of bacteria. It has been found that researchers have observed reduced LAB counts, both 2 to 4 log CFU/mL and concomitant yield enhancements both in laboratory and pilot-scale fermentation(50). More complex designs have also employed the inducible expression systems whereby the expression of bacteriocins can be induced under environmental conditions (pH changes or bacterial quorum-sensing molecules). This would decrease the metabolic burden of the production strain and provide particular antimicrobial coverage during the point of maximum risk of contamination(53).

Application of Bacteriocin-Producing Bacteria as Co-Cultures or Protective Cultures: In other processes, non-fermentative, bacterial form, LAB (e.g., *Lactococcus lactis* that produces nisin) can be included as a protective culture(54). They are not in competition with sugars but are vigorous in the inhibition of contaminants(55). The issue lies in making sure that they do not have a detrimental effect on the main fermenter and add to the lack of nutrients(56). Such strains that utilize a limited amount of substrate and had a controlled population dynamic must be carefully selected. Properly optimized protective cultures have the capability to offer sustained antimicrobial pressure and decrease dependence on chemical antimicrobials or antibiotics(57).

Enhancing Biobutanol (ABE) Fermentations

Clostridium acetobutylicum fermentation of ABE is infamously susceptible to bacteriophage infection and contamination by other bacteria, including other species of *Clostridium* which are less productive in solvent production or which switch their metabolite expression to acidogenesis in place of solventogenesis(58).

Targeting Competitive Microflora: The microbial community can be shaped with the help of bacteriocins that are active against clostridia(59). An example is the use of nisin and subtilin which would work against most species of *Clostridium*. They can also be used to suppress non-productive clostridia that provide a competitive edge to the production strain and aid in the maintenance of solventogenic metabolism(60). Microbial steering is especially appropriate with continuous or repeated-batch fermentation systems, where changes in the microbial communities can gradually reduce productivity.

Mitigating Phage Infections: Some bacteriocins also have been noted to induce stress or change membrane properties in their biologic hosts, reducing phage adsorption vulnerability. In other cases, direct blocking of phage receptors by exposure to bacteriocins has direct effects of lowering infection rates. This supportive effect, though indirectly acting, and strain-dependent, is a relevant secondary defence mechanism of phage-mediated process failure in industrial acetone-butanol-ethanol (ABE) fermentations(61).

Lignocellulosic Biofuel Fermentation Processes Applications.

Some of the new challenges brought about by the second-generation feedstocks include the presence of inhibitory compounds like furfurals, hydroxymethylfurfural

(HMF), weak organic acids and lignin derived phenolic compounds, and more heterogeneous consortium is introduced to the further pretreatment and hydrolysis of biomass(62).

Regulation measures against Contaminants in Inhibitor-Laden Environment: Investigations prove that particular bacteriocins retain their antimicrobial effects in the presence of lignocellulosic inhibitors, which makes them suitable in more challenging conditions of working (63). Their use can help to reduce the risk of contamination during simultaneous saccharification and fermentation (SSF) or consolidated bioprocessing (CBP), during which the increased residence times and co-culture of microbes increases the risk of contamination. Besides, bacteriocins can reduce the need to use harshly performed chemical sterilization protocols that might increase the production of inhibitors(64).

Engineering Robust Production Strains: The fermentative microorganisms (e.g., *Zymomonas mobilis*) with bacteriocin-producing strains of the bacterium are of particular use in consolidated bioprocessing (CBP) configurations where fermentative agents are in co-culture with enzyme-producing microbial consortia, increasing the chances of contamination(65). Incorporations of bacteriocin gene clusters into industrial strains may result in the self-protective biocatalysts that are capable of suppressing bacterial competition and maintaining a high fermentation rate at the same time. In combination with inhibitory compound tolerance engineering and ethanol, this strategy forms the basis of the generation of very robust microbial systems to produce biofuels based on lignocellulosic sources(66).

3. Results and Discussion

Production, Formulation, and Economic Considerations

To be adopted in industries, production and delivery should be cost effective. Also scalability, regulatory adherence and homogeneity of antimicrobial activity during industrial operating conditions are the key factors to successful application of bacteriocins as biocontrol in fermentations of biofuels(67).

Fermentation and Downstream Processing

GRAS LAB is optimally fermented to produce large quantities of bacteriocin. More than 70 percent of total cost can be represented by downstream processing (recovery, concentration, purification). The studies are concentrated on cost-effective media (e.g., whey, molasses), constant fermentation technology, and less complex recovery processes (e.g. adsorption desorption, precipitation, ultrafiltration) to lower costs (68).

Besides this, metabolic optimization methods, including the pH-controlled fed-batch fermentation, quorum-sensing stimulation, and genetic diversity of biosynthetic gene clusters have been investigated to raise the levels of bacteriocin and productivity. It has also been suggested that co-production of bacteriocins with primary fermentation products, e.g. lactic acid or ethanol, can be used to enhance overall process economics. Moreover, immobilized-cell systems provide extended bacteriocin generation with lesser idle time and enhanced operational stability and hence appeal to continuous industrial processes(69).

Formulation for Stability and Activity

Fermentation broths are complicated. Bacteriocins can be inactivated by proteases, changes in pH, adsorption on the feedstock solids and by reaction with ions. Some of the formulation strategies are microencapsulation, immobilization on carriers, and development of protective blends with chelators (e.g., EDTA) or other antimicrobials to increase stability and activity during the fermentation cycle.

Nanocapsules that are more advanced like those of alginate or chitosan have proven their increased resistance to degradation by enzymes and the controlled release of bacteriocins to changing PH and temperature environments. Also, a combination of bacteriocins with moderate heat treatment, organic acids, and bacteriophages can be

synergistically antimicrobial, which can be achieved with lower effective doses and low chances of developing resistance. Such methods of formulation are especially significant in lignocellulosic fermentations where deactivating or adsorbing free peptides can be caused by inhibitory compounds and suspended solids(70).

Economic Viability

Although the prices of purified bacteriocins are possibly now more expensive than virginiamycin, in-situ manufacture method through engineered strains removes purification expenses. The total cost-benefit analysis should include boosted yields, decreased downtime and the premium price in the market of antibiotic-free processes and co-products (animal feed).

The other economic benefits are less regulatory pressures on antibiotic residues, enhanced sustainability profiles, and in line with the circular bioeconomy approaches through the fermentation of waste substrates in mediums. According to the studies by life cycle assessment (LCA), the substitution of chemical antibiotics with naturally produced antimicrobials can contribute to the major reduction of environmental effects, such as greenhouse gas emissions and ecotoxicity. However, uptake by industry will be subject to the ability to prove the reliability of the process over the long term, the reproducibility of antimicrobial effect, and regulatory acceptance of strains of genetically modified production where needed.

Synergistic Approaches and Broader Bioprocess Applications

Bacteriocins have had little application as standalone agents in sophisticated contamination management techniques. Rather, they are being integrated into multilayered antimicrobial systems that are aimed at supplementing efficacy and cutting of required doses and preventing the development of resistance. The combined solutions are in line with the modern bioprocess engineering paradigms which focus on robustness and resilience of the processes, as opposed to single-point interventions(70).

Synergy with Other Antimicrobials

When used in combination with organic acids, as acetic and lactic acids, with plant essential oils and in combination with other bacteriocins, bacteriocins are synergistic. This synergism allows use of smaller dosages of each antimicrobial agent thus lowering the production cost and the chances of developing resistance (71). The organic acids undermine the integrity of bacterial cell membrane and increase its permeability that enables the entry and pore-forming activity of bacteriocins. Similarly, the constituents of essential oils such as thymol and carvacrol interfere with proton gradients and destabilize membranes and, thus, increase the lethality of bacteriocins even in sub-inhibitory levels.

In addition, the combination of bacteriocins and other peptides that bind different cellular receptors can expand the antimicrobial spectrum, and selectivity to particular contaminants can be maintained. So-called cocktails of bacteriocins are especially useful in industrial fermentations, where biocommunities are heterogeneous and dynamic, and where individual treatments using single bacteriocin agents might not be effective in managing all the problematic species(34).

Hurdle Technology

Combinations of bacteria and mild heat treatment, low pH acidification, or pulsed electric fields (PEF) lead to a multi-target, highly effective contamination management procedure. The concept of hurdle technology means that the individual responses of microorganisms to each of the interventions are sub-lethal; but once they are combined, they cause cumulative effects that are beyond those of each intervention alone. As example, momentary heating or PEF can be used to increase membrane permeability, which leads to bacteriocin permeation and faster cellular death(72).

This would allow the implementation of less harsh physical treatments that do not destroy fermentative microorganisms but at the same time reduce energy use compared with full sterilization. More importantly, the presence of hurdle systems also helps to reduce the selective pressure to resistance evolution as microorganisms are forced to co-

evolve to multiple independent stress mechanisms which is the state that can be referred to as a high evolutionary burden.

Fermentation in other industrial applications: Beyond Biofuels.

The principles that serve as the basis in bacteriocin-based biocontrol can be easily applied to a wide spectrum of non-sterile or semi-sterile bioprocesses. Examples of such applications include biosynthesis of organic acids- lactic, succinic, and acetic acids- industrial enzymes, amino acids and biopolymers such as polyhydroxyalkanoates (PHA). In both these scenarios it can be seen that bacterial population contamination is able to similarly redirect substrates towards its metabolic path, produce inhibitional metabolites and in turn reduce the total product titres(73).

Bacteriocins are also useful in the stabilisation of mixed microbial consortia and inhibition of opportunistic strain growth in the manufacture of probiotic and starter cultures. Furthermore, in continuous fermentation systems and immobilised-cell reactors, prolonged operational periods increase the chances of microbial contamination; in this case bacteriocins may ascertain prolific antimicrobial pressure minus the presence of any toxic residues or the regulatory overhead that are characteristic of more traditional antibiotics.

All these expanded uses highlight the adaptability of bacteriocins as platform biocontrol agents in the biotechnology industry. Their applicability is even much greater than the biofuel production and their role in the sustainable and antibiotic free manufacturing processes is confirmed(74).

Challenges and Future Perspectives

However, despite the hope that comes along with bacteriocins, there are quite high challenges. Although bacteriocins represent a biologically elegant and environmentally harmless substitute to traditional antimicrobials, a number of scientific, technical and regulatory challenges need to be cleared before it can be used widely on an industrial basis.

Scientific and Technical Challenges

Narrow Spectrum: As the microbiome is being preserved, the use of bacteriocins might require the creation of custom-made cocktails in order to offer a wide-spectrum coverage. The strain selectivity of many bacteriocins limits their isolated performance in complex industrial fermentations which in many cases harbor multiple contaminant species at the same time. This in turn necessitates the formulation of multi-bacteriocin forms or the combination of bacteriocins with other antimicrobials; this predisposes complexities in formulation, dosing and regulatory approval(75).

Resistance Development: Although the rate of resistance development in bacteriocins is relatively low compared to the rate when using traditional antibiotics, cases have been reported in which bacteria adapted to them by cell envelope reorganization or efflux regulation, and so this indicates that special attention should be paid to its development. Mechanistic pathways include changes to membrane charge, progressions of bacteriocin receptors, and expression of stress-response pathways. Selective pressure during continuous or repeated-batch fermentation can encourage the expression of tolerant sub-populations and so the need to adopt rotational approaches, combinations and dynamically-adjusted dosing schedules to alleviate the emergence of resistant phenotypes(76).

Regulatory Approval: Every new bacteriocin or genetic engineered strain requires extensive safety assessment, to be used in food, feed and environmental situations including complying with Good Manufacturing Practice (GMP) requirements. Various jurisdictions take different regulatory routes depending on the method of introducing the bacteriocin, either in purified forms, by locating the production on genetically modified organisms (GMOs), or by exposure to protective cultures. Such critical concerns as horizontal gene transfer, ecological persistence, and occupational exposure should be assessed strictly, which may slow down commercialization and increase development

costs. In addition, scalability still remains a technical bottleneck. The efficacy in the laboratory never turns into industrial performance due to matrix effects, adsorption to biomass or solids, enzymatic degradation, and dilution in large fermenters. As a result, compatibility and stability of processes under conditions of the actual fermentation should be confirmed at pilot and at full industrial level(77).

Future Research Directions

Discovery of novel biogenic bacteriocins: The recent metagenomic and genome-mining technologies have demonstrated the discovery of novel bacteriocins with different spectra and physicochemical properties in under-studied environments. The current developments in the fields of bioinformatics and machine-learning methods are increasing the rate of discovery of the cryptic groups of bacteriocin genes, most of which encode peptides with new structural motifs and modes of action. These findings have the potential to broaden the antimicrobial activities against demanding industrial pollutants, such as lactic acid bacteria and clostridial species that are resistant to antimicrobials(78).

Protein engineering, including rational design and directed evolution, may be used to modify bacteriocins to improve their stability at acidic or high-temperature, increase their antimicrobial range, and increase their efficacy. Peptide-membrane interaction Structural clarification of peptide-membrane bonds allows precise replacement of amino acids to enhance membrane affinity and enhance resistance to proteolytic breakdown and enhance solubility. Besides this, the possibility of hybrid bacteriocins to be formed by modular peptide engineering creates the way to the fusion of functional domains of different bacteriocins resulting in the most successfully engineered chimeric product(79).

Systems and Synthetic Biology: Self-protection of engineered strains of industrial strength such as *Saccharomyces cerevisiae* and *Clostridia* spp. is achieved through the provision of an integrated, regulated system of bacteriocin and resistance markers. To reduce the metabolic load associated with regular fermentation processes, development of “kill-switch circuits, which triggers bacteriocin production only when contaminants are detected, can be used, and antimicrobial defense can be induced only when contamination is detected. Adaptive self-regulating contamination controls can be offered by synthetic gene circuits using quorum-sensing or stress promoters. Also, co-design of production strains and bacteriocin expression systems can be used to increase the resilience of processes, allowing fermentations to be run with weaker sterilization regimes. This will minimize the operating expenses and the use of energy(80).

The association of bacteriocin application with on-line, real-time monitoring of contaminant biomarkers makes automatic intervention very specific. New biosensors using optical, electrochemical, or molecular detection principles have the potential to detect the early signs of contamination (organic-acid spikes or microbial metabolites). By combining these indicators with automated dosing or induction, intelligent, responsive control of bioprocesses would become attainable and the application of bacteriocin would be altered in its current state of merely supplementation and a contamination-management approach would be created.

4. Conclusion

The possibility of microbial contamination is one of the basic limitations of the economic feasibility of biofuel production in industry. Avoiding this challenge is highly challenging, and environmental and natural antimicrobials like bacteriocins are a formidable force capable of reducing it. It has been proven that with the assistance of experimental evidence, bacteriocins are highly effective in suppressing major contaminants in both laboratory and pilot-scale fermentations, hence generating quantifiable changes in product yield. The most promising approach towards the future development of this area is not based on the mere accumulation of bacteriocins but on the novelty of implementing the biosynthetic production of bacteriocins into the biocatalyst itself via metabolic engineering and in this way, producing self-defending production

strains. Although cost, stability and regulatory compliance challenges have lingered, interdisciplinary convergence between microbiology, synthetic biology and process engineering is fast providing solutions to the challenges. The whole introduction of bacteriocin-based biocontrol interventions can thus be considered a bold move in the direction of building more consistent, efficient and sustainable industrial bioprocesses, which, in the end, makes the principles of the global bioeconomy even stronger.

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